## Highly active gold-based catalyst for the reaction of benzaldehyde with ethyl diazoacetate

Manuel R. Fructos, M. Mar Díaz-Requejo\* and Pedro J. Pérez\*

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The gold complex [IPrAu(NCMe)]BF<sub>4</sub> catalyzes the reaction of ethyl diazoacetate with benzaldehyde to give mixtures of ethyl 3-oxo-3-phenylpropanoate and ethyl 3-hydroxy-2-phenyl-acrylate in the first example of a group 11 metal-based catalyst for this transformation; the catalyst activity is improved by a factor of 2500 compared to those of previously reported iron-based catalysts.

The thermal reaction of ethyl diazoacetate with benzaldehyde was first described<sup>1</sup> in 1885 by Buchner and Curtius and the products correctly proposed later by Dieckmann as 1,3dioxolanes (Scheme 1a).<sup>2</sup> Nearly a century after the seminal work, Huisgen and De March described<sup>3</sup> the use of copper and rhodium as catalysts for the reaction of diazomalonate with benzaldehyde to give a mixture of dioxolanes (Scheme 1b). Since then, several synthetic procedures based on the use of a diazoacetate and an aryl-aldehyde,<sup>4</sup> have been described (Scheme 2). Thus, acid- or base-catalyzed systems led to the formation of  $\beta$ -ketoesters,<sup>5</sup> derived from the formal insertion of the carbene moiety into the aldehydic C-H bond (Scheme 2, i). A second type of transformation is an aldol-type addition,<sup>6</sup> promoted by base or by a transition metal complex, the diazo functionality being retained in the final product (Scheme 2, ii). The addition of the carbene group to the carbon-oxygen double bond of the aldehyde to give oxiranes has also been observed in a few cases (Scheme 2, iii).<sup>7</sup> Very often, the use of rhodium-based catalysts has led to the formation of oxolanes (Scheme 2, iv),<sup>8</sup> whereas in the case of iron-catalysts, 3-hydroxy-2-arylacrylic acid esters along with  $\beta$ -ketoesters have been reported (Scheme 2, i, v).<sup>9,10</sup>

The synthesis of the acrylic ester shown in Scheme 2 is of interest since it is a precursor of naproxen or tropic acid.<sup>11</sup> We



Laboratorio de Catálisis Homogénea, Departamento de Química y Ciencia de los Materiales, Unidad Asociada al CSIC, Universidad de Huelva, Campus de El Carmen, 21007-Huelva, Spain. E-mail: mmdiaz@dqcm.uhu.es, perez@dqcm.uhu.es; Fax: + 34 959 219942; Tel: + 34 959 219956



Scheme 2 Possible products of the reaction of ethyl diazoacetate (EDA) and benzaldehyde.

are aware of only a few systems capable of inducing such a transformation. Iron-based catalysts developed by Hossain and co-workers<sup>9a</sup> provided mixtures of both ethyl 3-oxo-3-phenylpropanoate (1) and ethyl 3-hydroxy-2-phenylacrylate (2) (eqn (1)). The use of Lewis acids as catalyst led<sup>9b</sup> to similar results, although the maximum 1:2 ratio (31:69) was achieved with [CpFe(CO)<sub>2</sub>(thf)]BF<sub>4</sub>. Further work by Kirchner and co-workers<sup>10</sup> using the [Fe(PNP)(CO)(CH<sub>3</sub>CN)<sub>2</sub>](BF<sub>4</sub>)<sub>2</sub> (PNP = diphosphine–pyridine pincer ligand) complex as the catalyst gave a *ca*. 3:97 ratio of products, in the most selective system reported to date for this transformation. Kanemasa *et al.* also described the use of Lewis acid catalysts to give mixtures of 1 and 2.<sup>12</sup>



The use of gold-based catalysts for the transfer of carbene groups from diazo compounds is yet limited to a few examples.<sup>13</sup> Our group has recently described the first examples of gold-based catalysts of general formulae (NHC)AuCl (NHC = *N*-heterocyclic carbene ligand) for such transformations, applied to sp<sup>2</sup>- and sp<sup>3</sup>-C-H bond functionalization<sup>14,15</sup> as well as to olefin cyclopropanation,<sup>16</sup> other examples being reported by other groups.<sup>17</sup> We then became interested in exploring the catalytic capabilities of the complexes in the reaction of benzaldehyde with ethyl diazo-acetate. In a series of screening tests, three complexes of type (NHC)AuCl<sup>18</sup> containing the ligands IPr, IMes and SIPr were employed as catalyst precursors in the reaction of



Scheme 3 (NHC)AuCl complexes as catalysts in the reaction of EDA with benzaldehyde.

benzaldehyde with ethyl diazoacetate (Scheme 3). After 24 h of stirring at room temperature, compounds 1 and 2 were detected in the reaction mixture, although most of the ethyl diazoacetate (EDA) remained unconsumed.

Since we have previously established that the catalytic species when using these gold complexes are cationic in nature.<sup>14-16</sup> derived from the removal of the halide by a non-coordinating counterion, we decided to test the catalytic capabilities of the complex [IPrAu(NCMe)]BF4,<sup>19</sup> prepared by the direct reaction of IPrAuCl and AgBF4 in acetonitrile as the solvent.<sup>†</sup> To our delight, the use of this complex as catalyst in the reaction of EDA with benzaldehyde afforded quite interesting results (eqn (2)). Thus, when EDA (1 mmol) was added to a methylene chloride solution of benzaldehyde (5 mmol) containing 0.01 mmol of [IPrAu(NCMe)]BF4, instantaneous evolution of gas was observed, due to the release of dinitrogen from ethyl diazoacetate. GC studies after 10 min of stirring at room temperature demonstrated the complete consumption of EDA, although it is very likely that the EDA was consumed instantaneously. NMR studies of the crude reaction mixture allowed the identification of the products formed in this transformation as 1 and 2 in a 30:70 ratio, respectively. No diethyl fumarate or maleate, the products derived from the catalytic coupling of EDA, were observed in the NMR detection limit, in spite of the addition of all the diazo compound in one portion at the beginning of the reaction. When EDA was employed in excess, unreacted EDA was recovered at the end of the reaction. A preparative scale experiment carried out with a 1:300:1500 ratio of [Au]: [EDA]: [PhCHO] led to the isolation of both products in 95% isolated yield, based on initial EDA. Interestingly, only 10 min were required for all the EDA to be consumed.



We have also investigated the effect of the benzaldehyde: EDA ratio in the final distribution of products, 1:2. As shown

**Table 1** Reaction of EDA and benzaldehyde in the presence of  $[IPrAu(NCMe)]BF_4$  as the catalyst<sup>*a*</sup>

Entry	Temperature/ $^{\circ}C$	[PhCHO]/[EDA]	% 1	% 2	
1	rt	0.5	45	55	
2	rt	1	40	60	
3	rt	2	35	65	
4	rt	5	30	70	
5	rt	10	30	70	
6	$-80^{b}$	5	15	85	
7	0	5	33	67	
8	+80	5	52	48	

<sup>*a*</sup> Catalyst loading = 1% referred to EDA, 0.01 mmol of [Au]. Reaction time 10 min. <sup>*b*</sup> Reaction time 7 h.



Fig. 1 Effect of the [PhCHO]: [EDA] ratio on the selectivity.

in Table 1, the use of higher amounts of benzaldehyde relative to EDA induced a slight increase in the yield of the acrylate derivative, although the 30:70 mixture of 1:2 seems to be the limit achievable with this catalyst (Fig. 1). Since it would be interesting to control the selectivity of this transformation towards the formation of **2**, we wondered about the effect of the temperature in this transformation. Therefore, experiments at -80, 0 and +80 °C were performed, with a clear trend extracted from them: lowering the temperature favours the formation of the acrylate **2** whereas an increase in temperature is accompanied by an augmentation of the relative amounts of the ketoester. In the lower limit explored at -80 °C, the relative ratio of products 1:2 was determined as 15:85.

To the best of our knowledge, this is the first example of the use of a group 11 metal-based catalyst for this transformation that leads to the formation of acrylate 2. Only copper had been previously reported to give either oxolanes<sup>8</sup> or β-ketoesters,<sup>5</sup> and gold remained yet undiscovered for this reaction between benzaldehyde and EDA. The selectivity of this gold catalyst at room temperature is similar to that of Hossain's catalyst<sup>9</sup> and far from Kirchner's catalyst.<sup>10</sup> However, it is remarkable that the reaction rate and the turnover frequency are higher than those for the reported iron catalysts. The catalyst loadings for Fe-based systems were 10%, and reaction times reached 14-16 h,9,10 leading to TOF values, measured as [(mmol EDA consumed)/[(mmol catalyst)  $\times$  (reaction time)], of 0.6-0.7. Our gold-based catalyst is remarkably active, with a TOF value of 1800, ca. 2500 times faster than the Fe-based catalysts.

**Table 2** Reaction of ethyl diazoacetate (EDA) with benzaldehyde inthe presence of  $[PPh_3Au(NCMe)]BF_4$  as the catalyst<sup>a</sup>

Entry	Temperature		[PhCHO]/[EDA]			]	% 1	% 2	
1	rt		2				57	43	
2	rt		10				33	67	
<sup>a</sup> Catalyst	t loading	= 1%	referred	to	EDA,	0.01	mmol	of [Au]	

Reaction time, 10 min.

We have also explored a related catalyst that contains the phosphine PPh<sub>3</sub> instead of the NHC ligand. The [PPh<sub>3</sub>Au(NCMe)]BF<sub>4</sub> complex was prepared as previously described<sup>20</sup> and employed following the procedure identical to that used with the NHC-containing catalyst. Two experiments with two- and ten-fold excesses of benzaldehyde with respect to EDA were carried out (Table 2). In both cases, all the diazo compound was consumed within 10 min, also showing a high catalytic activity. Regarding the selectivity, the system behaves in a similar manner when using a ten-fold excess of benzaldehyde (entry 5 Table 1 and entry 2 in Table 2), but when lowering such excess, the phosphinecontaining catalyst provided more of the ketoester 1 than the NHCAu catalyst (entry 3 in Table 1 and entry 1 in Table 2). Therefore, it seems that the change from IPr to PPh<sub>3</sub> in the catalyst structure does not affect the activity but induces a certain effect on the selectivity.

In conclusion, we have discovered that the complex [IPrAu(NCMe)]BF<sub>4</sub> catalyzes the reaction of PhCHO and ethyl diazoacetate leading to the formation of ethyl 3-hydroxy-2-phenylacrylate and ethyl 3-oxo-3-phenylpropanoate, the former being the major product. The reaction rates are extremely high, in comparison with previously reported systems. Mechanistic studies to elucidate the nature of this transformation are currently underway in our laboratory.

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## Notes and references

† Experimental procedures. The complexes (NHC)AuCl and [IPrAu(NCMe)]BF<sub>4</sub><sup>18,19</sup> were prepared according to literature methods. EDA and benzaldehyde were purchased from Aldrich, and employed without further purification. Solvents were dried prior to use. NMR spectra were recorded using a Varian Mercury 400 MHz. Catalysis procedure: in a Schlenk tube, under a dinitrogen atmosphere, 0.01 mmol of the catalyst was dissolved in 3 mL of CH<sub>2</sub>Cl<sub>2</sub> along with the desired amount of benzaldehyde. Ethyl diazoacetate was added in one portion *via* microsyringe. Immediate evolution of gas was

observed. After 10 min of stirring, no EDA was detected by GC. Volatiles were removed under vacuum and the residue dissolved in  $CDCl_3$  and investigated by NMR spectroscopy. The compounds were identified by comparison with pure commercial samples and/or literature data. It is important to note that both compounds 1 and 2 display tautomeric equilibria in solution, the resonances of the keto and enol forms being taking into account when calculating the ratio of products.

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